Applicants have hereinabove amended claims 44, 46 and 47. Support for the amended claims may be found inter alia in the specification on page 12, lines 23-26. Applicants maintain that amended claims 44, 46 and 47 do not involve any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter amended claims 44, 46 and 47.

Applicants have further amended the specification to correct for minor, obvious clerical or typographical errors. Applicants have clarified the description of the figures to refer to specific figures. Applicants maintain that the amendments do not introduce new matter to the subject application. Accordingly, applicants respectfully request entry of these amendments.

The Examiner stated that the disclosure is objected to because of the following informalities: On page 5, line 30, in Brief Description of the Figures, Figure 6B is listed as IgG antibodies but Figure 6B has the y-axis labeled as IgG titer.

In response, applicants will submit a revised Figure 6B correctly labeling the y-axis as IgG when this case is in condition for allowance. Accordingly, applicants respectfully request that the Examiner withdraw and reconsider the objection to the specification.

Rejection Under 35 U.S.C. §101

The Examiner stated that claims 44-56 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 44-46 of copending application Serial No. 08/481,809. The Examiner stated that this is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The Examiner stated that the claims 44-56 of this application

conflict with claims 44-56 of application serial number 08/481,809. 37 C.F.R. 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. The Examiner stated that the applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications.

The Examiner stated that the claims 44-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, and 44-52 of copending application. Serial Nos. 08/475,784, and 08/477,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art at the time of the invention to use the composition set forth in the claims recited in the copending application in the method as instantly claimed since the composition as recited in the copending application is described as a vaccine.

The Examiner stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to the provisional double patenting rejection, applicants point out that the claims of the subject invention is directed to a method of using a ganglioside conjugate vaccine, wherein the ganglioside is selected from the group consisting of GM2, GM3, GD2, GD3, GD3 lactone, O-Acetyl GD3 and GT3. In contrast, the claims of U.S. Serial No. 08/481,809 are broadly directed to a method of using ganglioside conjugate vaccine.

Accordingly, the claims of the subject application are narrower

in scope than the claims of U.S. Serial No. 08/481,809. As provided in M.P.E.P. §706.03(k), "a mere difference in scope between claims has been held to be enough" to overcome a double patenting rejection. Further, the claims of the subject application could be infringed in various ways without infringing the claims of U.S. Serial No. 08/481,809. Thus, the test for double patenting as defined in M.P.E.P. §804 leads to the conclusion that the claims do not conflict and the double patenting rejection is improper.

Applicants further point out that for a provisional double patenting rejection, M.P.E.P. §804 requires that the:

> 'provisional' double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the application(s) into a double patenting rejection at the time the one application issues as a patent.

Therefore, applicants maintain that even if the Examiner continues to conclude that the claims of the subject application conflict with the claims of U.S. Serial No. 08/481,809, the provisional rejection should be withdrawn in view of applicants' arguments which overcome the other rejections of this application under Sections 103 and 112. Thus, the subject application should be allowed to issue.

<u>Rejection Under 35 U.S.C. §112, second paragraph</u>

The Examiner stated that claim 49 is rejected under 35 U.S.C.

112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claim 49 is vague and indefinite for using the trademark "QS-21" since it is unclear what the metes and bounds of said trademark. The Examiner stated that since a product denoted by a trademark may at some time change it is suggested the trademark be accompanied with the generic terminology.

The Examiner stated that the claim 49 is indefinite because it contains the abbreviation "QS-21". The Examiner stated that full terminology should be in each instance in the claims without the additional use of redundant abbreviations in parentheses or otherwise.

In response, applicants respectfully traverse the 35 U.S.C. §112, second paragraph rejection of claim 49. Applicants respectfully point out that QS-21 is not a trademark name of the aforementioned adjuvant. As discussed in Kensil, et al. (1991) J. Immunology 146: 433, QS-21 refers to an isolated sample of Quil-A, a commercial saponin derived from *Quillaja saponaria* Molina, commonly used in adjuvant studies, which was isolated by high-pressure liquid chromatography. Thus, the term "QS-21" is neither vague nor indefinite because the compound was well-known in the art prior to the filing of the application. Further the specification states on page 20, lines 13-14, that QS-21 is a saponin component of Quil-A. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. §112 rejection of claim 49.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 44-56 under 35 U.S.C. 112, first

paragraph.

The Examiner stated that the specification teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines. The Examiner stated that the specification also teaches that immunization of mice with the GD3-Keyhole Limpet Hemocyanin (GD3-KLH) conjugate generated the highest titer of IgM and IgG responses compared to the other conjugates tested and that the sera was highly specific for GD3 in human tissue extracts. The Examiner stated that the specification teaches that melanoma patients immunized with the GM2-KLH generated high titers of IgM and IgG antibodies. The Examiner stated that the specification does not teach that the production of antibodies to GD3-KLH or GM2-KL results in the treatment of the cancer. The Examiner stated that the production of antibodies upon administration of a ganglioside conjugate vaccine cannot be extrapolated to the ability of the antibodies to prevent or treat cancer since in a previous study (Fung, et al.), no significant prolongation of survival was observed in mice that were administered a GM2-KLH conjugate vaccine, despite the ability of GM2-KLH to produce of high titers of anti-GM2 IgG antibodies. Therefore, the Examiner stated that the production of antibodies upon administration of a ganglioside conjugate vaccine is not sufficient to insure that these antibodies will also prevent or treat cancer.

In response, applicants respectfully traverse the Examiner's rejection based on the above-stated grounds.

Fung, et al. disclose active specific immunotherapy of a murine mammary adenocarcinoma using a synthetic tumor-associated glycoconjugate. The Fung, et al. experiment is not a study to evaluate GM2-KLH conjugated vaccine. There is no evidence in Fung, et al. to show that the cancer cells studied express GM2. Fung, et al. did not measure GM2 antibodies generated from the GM2-KLH conjugated vaccine. In fact, the GM2-KLH conjugated

vaccine was used as unrelated hapten to exclude nonspecific effects (see page 4310 of Fung, et al.) Therefore, the Fung, et al. experiments were not designed to study whether the GM2-KLH conjugated vaccine prolonged survivability. Accordingly, Fung, et al. experiments should not be used to question whether antibodies generated against the ganglioside conjugate vaccines will prevent cancer.

The Examiner stated that the specification also does not provide guidance on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. As described in the specification the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. The Examiner stated that due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides. The Examiner stated that the specification also does not provide guidance on the synthesis of derivatives of KLH not does the specification teach which derivatives would result in an enhanced antibody response.

In response, applicants hereinabove amended claims 44, 46 and 47 to be drawn to methods comprising a vaccine which is capable of the producing "an antibody which recognizes a ganglioside, comprising an amount of ganglioside, which is selected from the group consisting of GM2, GM3, GD2, GD3, GD3 lactone, O-Acetyl GD3 and GT3, or oligosaccharide portion thereof..." Applicants' amended claims 44, 46 and 47 to recite methods comprising a vaccine, wherein the ganglioside of the vaccine is selected from the group consisting of GM2, GM3, GD2, GD3, GD3 lactone, O-Acetyl GD3 and GT3. All of these gangliosides are capable of being conjugated to an immunogenic protein at the ceramide portion. As discussed in the specification on page 18 line 35-page 19,

line 8, most importantly, all of these gangliosides maintain the integrity of the oligosaccharide portion after conjugation to the immunogenic protein. Using the materials and methods disclosed on page 21, line 29-page 23, line 19; page 24, line 15-page 26, line 25, line 32; page 43, line 26-page 50, line 11, one skilled in the art could produce a conjugate comprising an immunogenic protein and a ganglioside that retains its antigenicity. Therefore, the specification provides enough information to enable one skilled in the art to practice the claimed method comprising a vaccine capable of producing an antibody comprising a ganglioside-immunogenic protein conjugate.

Applicants also point out that one skilled in the art has the requisite knowledge to synthesize derivatives of KLH capable of inducing an immune response in the subject method of use. Further, applicants point out that the specification provides enough information to one skilled in the art to determine which derivatives of KLH would be effective in the subject vaccine. In the specification, applicants disclose specific immunogenic proteins, other than KLH, that were conjugated to the ganglioside, e.g. MAP, OMP, cBSA and KLH (see page 19, lines 9-13 of the specification) and produced an IgG immune response. Therefore, the specification enables one skilled in the art to construct a vaccine which is used in the subject method.

Accordingly, applicants respectfully request that Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph. Further, applicants respectfully request that the Examiner allow pending claims 44 and 46-56.

<u>Rejection Under 35 U.S.C. §103</u>

The Examiner stated that the claims 44-48, and 53-56 are rejected under 35 U.S.C. §103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et

al (U.S. Pat. No. 5,102,663) and Ritter et al (1990).

The Examiner stated that Livingston et al. teach a vaccine administered to melanoma patients for stimulating the production of antibodies directed 5 against a carbohydrate epitope on the ganglioside, GM2. The Examiner stated that Livingston et al teach that the vaccine is administered at a concentrations of 100, 200, or 300 μg with an adjuvant, Bacillus Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline. The Examiner stated that Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination. The Examiner stated that Livingston et al. teach that more patients produced IgM antibodies that IgG antibodies to the GM2. The Examiner stated that Livingston et al. also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas. The Examiner stated that Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). The Examiner stated that Livingston et al also do not teach the use of any other gangliosides in a vaccine preparation.

The Examiner stated that Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response. The Examiner stated that Ritter et al discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. The Examiner stated that Livingston et al (U.S. Pat. No. 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of

neuroectodermal origin. The Examiner stated that Ritter et al (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic that GD3.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages taught above by Ritter et al (1991). The Examiner stated that it would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston et al (U.S. Pat 5,102,663) and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. It would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990), and would be expected to produce and enhanced antibody response compared to GD3.

The Examiner stated that the optimization of the dosage, route of administration, and number of sites to administer the composition is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's §103 rejection. The subject invention is neither disclosed, taught, or suggested, individually or in combination, by the cited references.

Individually, the cited references do not make the subject invention obvious. Livingston, et al. discuss immunizing melanoma patients with a vaccine composed of a ganglioside, GM2,

mixed with BCG. Livingston, et al. do not disclose or teach a ganglioside conjugate vaccine, and therefore this article does not disclose or teach the claimed invention.

Ritter, et al. (1990) do not suggest or motivate one skilled in the art to practice the subject invention. Ritter, et al. disclose GD3 derivatives, specifically GD3 lactone, induced antibody responses in mice.

Ritter, et al. (1991) does not disclose applicants' method of conjugating a ganglioside to an immunogenic protein. The applicants' specification clearly teaches the importance of maintaining the integrity of the oligosaccharide portion of the ganglioside. Ritter, et al. (1991) do not disclose the use of adjuvants in optimizing the immune response. Applicants' claimed invention comprises an effective amount of adjuvant. Accordingly, Ritter, et al. (1991) do not teach the applicants' claimed invention.

It has been known in the prior art that results obtained from animals studies are not predictive of the results in humans. Ritter, et al. (1991) performed their study only on mice. These results cannot be predictive of results in humans.

Livingston, et al. (U.S. Patent 5,102,663) discuss a specific vaccine composed of only the 9-O-acetyl GD3 ganglioside and an adjuvant. Livingston, et al. never disclose nor teach conjugation of a ganglioside with any immunogenic protein. Further, throughout the patent, the adjuvant QS-21 is neither disclosed nor suggested. Therefore, the patent neither discloses nor suggests the subject invention.

Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Accordingly, applicants respectfully request

that the Examiner reconsider and withdraw the above-stated grounds of rejection.

The Examiner stated that claim 49 is rejected under 35 U.S.C. 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) as applied to claims 44-48, and 53-56 above, and further in view of Kensil et al and Marciani et al. The Examiner stated that the teachings of Livingston, et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) are set forth above. The Examiner stated that the above cited art does not teach the use of QS-21 as an adjuvant.

The Examiner stated that Kensil et al teach that QS21 produced a higher antibody response that aluminum hydroxide. The Examiner stated that Kensil et al also teach that the immune responses obtained with QS21 reached a plateau at doses between 10 and 80 μg in mice. The Examiner stated that Marciani et al teach the use of QS21 as an adjuvant in a vaccine at concentrations of 10 and 20 μg. Marciani et al also teach that the QS21 adjuvant did not cause a toxic reaction in cats.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to add QS21 as an adjuvant to the vaccine taught by the above cited art because QS21 produces a higher antibody response than the commonly used adjuvant, aluminum hydroxide, as taught by Kensil et al, and QS21 is not toxic to animals as taught by Marciani et al. The Examiner stated that it would also have been obvious to use doses of between 10 and 200 μg because the immune response obtained with QS21 plateaus at doses between 10 and 80 μg and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's above rejection under 35 U.S.C. §103.

Applicants have already discussed Livingston, et al. (Cancer Res) and Ritter, et al. (1991) and Livingston, et al. (U.S. Patent 5,102.663) and Ritter, et al. (1990) hereinabove and would like to reiterate their prior statements regarding these references.

Neither Kensil, et al. nor Marciani, et al. disclose or teach applicants' claimed invention. Applicants further maintain that the other references cited by the Examiner in combination with these two references do not render the claimed invention obvious. Accordingly, applicants maintain that the claimed invention is patentable over the cited references, and respectfully request that the Examiner reconsider and withdraw the above-stated §103 rejection.

The Examiner stated that claims 51 and 52 are rejected under 35 U.S.C. 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) as applied to claims 44-48, and 53-56 above, and further in view of Irie et al.

The Examiner stated that the teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) are set forth above. The Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

The Examiner stated that Irie et al teach that the ganglioside

GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas. The Examiner stated that it would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

In response, applicants respectfully traverse the Examiner's rejection of claims 51 and 52 under 35 U.S.C. § 103. As discussed above, the teachings in Livingston, et al., Ritter, et al. (1991), U.S. Patent 5,102,663 and Ritter, et al. do not make the subject invention obvious. Irie, et al. does not disclose a ganglioside conjugate vaccine administered with an effective amount of adjuvants and a pharmaceutically acceptable vehicle. The teaching that the ganglioside GM2 is found on or in tumors of a variety of histological types, including melanoma and breast carcinomas" do not teach or motivate a person of ordinary skill in the art to practice the claimed invention. Even combining, Irie, et al. with the other cited references, one would not find the claimed invention obvious.

Accordingly, in view of the foregoing statements, applicants request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. §103. Applicants respectfully request that the Examiner allow claims 44 and 46-46.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $465 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. Applicants enclose a check in the amount of $465.00. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Albert Wai Kit Chan 12/10/96
Albert Wai-Kit Chan Date
Reg. No. 36,479